Docket No.: 124907.0111
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Janakraj MEHRA et al.

Application No.: 10/807,221 — Confirmation No.: 3311

Filed: March 23, 2004 — Art Unit: 1621

For: METOPROLOL MANUFACTURING PROCESS — Examiner: S. A. Barts

CLAIM FOR PRIORITY AND SUBMISSION OF DOCUMENTS

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Applicants hereby claim priority under 35 U.S.C. 119 based on the following prior foreign application filed in the following foreign country on the date indicated:

Country	Application No.	Date
India	1185/MUM/2003	January 7, 2004

In support of this claim, a certified copy of the said original foreign application is filed herewith.

Applicant believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 23-2185, under Order No. 124907.0111 from which the undersigned is authorized to draw.

Dated: January 29, 2008

Respectfully submitted,

By _____
Charles R. Wolfe, Jr.
Registration No.: 28,680
BLANK ROME LLP
Correspondence Customer Number: 27557
Attorney for Applicant

INTELLECTUAL
PROPERTY **INDIA**
बौध्दिक सम्पदा भारत
एकस्व /अभिकल्प /व्यापार चिन्ह /
भौगोलिक संकेत
PATENTS / DESIGNS /
TRADEMARKS /
GEOGRAPHICAL INDICATIONS

सत्यमेव जयते

भारत सरकार /GOVERNMENT OF INDIA
पेटेन्ट कार्यालय /THE PATENT OFFICE
बौध्दिक सम्पदा भवन, मुंबई -४००३७
Boudhik Sampada Bhavan
Near Antop Hill Post Office, S.M.Road ,
MUMBAI-400037

दूरभाष Tel ■ 022-24137701
फॅक्स Fax 🖷 022-24130387
Email patmum@vsnl.net
Website www. ipindia.nic.in

THE PATENTS ACT, 1970

IT IS HEREBY CERTIFIED THAT, the annex is a true copy of the Complete Specification filed on 07/01/2004 in respect of Patent Application No.1185/MUM/2003 of **(a) IPCA LABORATORIES LIMITED, (b) 48, Kandivli Industrial Estate, Mumbai – 400 067, Maharashtra, India, (c) Indian Company corporated under the Companies Act 1956.**

This certificate is issued under the powers vested in me under Section 147 (1) of the Patents A[illegible]970.

Dated this 24th day of January 2008.

(A.T. PATRE)
ASSTT. CONTROLLER OF PATENTS & DESIGNS.

FORM 2

COMPLETE AFTER PROVISIONAL
07.01.2004

THE PATENTS ACT, 1970
(39 of 1970)

COMPLETE SPECIFICATION

[See section 10; rule 13]

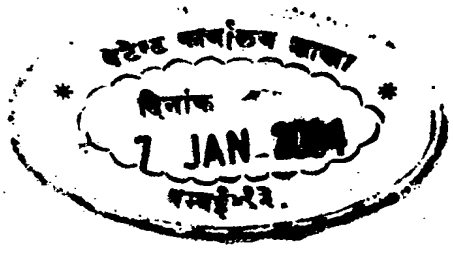
"An improved industrial process for manufacture of Metoprolol base and salts thereof"

(a) IPCA LABORATORIES LIMITED

(b) 48, Kandivli Industrial Estate, Mumbai – 400 067, Maharashtra, India

(c) Indian Company incorporated under the Companies Act 1956

The following specification describes the nature of the invention and the manner in which it is to be performed:



1185 | मुंबई MUM-2003

7 JAN 2004

An improved industrial process for manufacture of Metoprolol base and salts thereof

Technical Field of the invention:

This invention relates to an improved industrial process for manufacture of β-blocker, antihypertensive compounds more particularly Metoprolol base and salts thereof.

Background and Prior Art

Metoprolol and its salts such as tartrate and succinate are well established drugs having anti-hypertensive activity. These compounds acts as β-blockers. The patients suffering from hypertension needs to be on treatment by these drugs for the whole lifetime. This kind of therapy necessitates that; the drugs are of high purity with very less impurity levels, so that the side effect is minimum. It also demands to produce these drugs at cheaper prices.

Ample literature is available for producing metoprolol base and its salts, due to the significance of these compounds as anti hypertensive agents.

Spanish patent ES 2011584 (equivalent US Patent 5082969) describes a process for metoprolol, where 4-(2-methoxyethyl) phenol and epichlorohydrin are reacted in aqueous alkaline conditions at 0° - 25°C temperature for 15-20 hours. The organic phase consisting of epoxide is separated, washed with water and used as such for reaction with large excess of isopropylamine in aqueous media like water at 0° - 30°C temperature.

Polish Patent PL 158497 describes a process wherein 4-(2-methoxyethyl) phenol and epichlorohydrin are reacted at 20° - 80°C temperature for 3 hours under aqueous alkaline conditions. The epoxide so formed is reacted with large excess of isopropyl amine

(medium as well as reactant) to yield metoprolol base.

Nearest prior art to the present invention is the form of US Patent 6252113, discloses reaction between 4-(2-methoxyethyl) phenol and epichlorohydrin in aqueous alkaline conditions at 50° - 70°C temperature for 1 hour. The resulting epoxide is distilled under high vacuum to improve quality. Pure epoxide then is treated with isopropylamine in solvent such as isopropyl alcohol.

As has been seen, lot of knowledge in the present field of invention is available; however, there remain some problems, which lead the scope for further investigations. It can be seen that almost all prior art have reactants per se same. Reactions which are carried out at lower temperatures (below ambient) leads to slow rate of reaction with more impurity levels when the reaction at higher temperature range is carried out, the rate of reaction increased but required purification by distillation under high vacuum.

In the processes where purification of epoxide is avoided, the resultant products are formed with higher impurities. The processes involving excess use of isopropyl amine leads to increased costs. The products formed with higher impurity levels necessitate extra purifications, which enhances the costs.

Therefore, it is of importance to develop a process for manufacture of metoprolol base, which is economical, eco-friendly and yielding high quality with higher yields, which also avoids the operations like high vacuum distillation.

The patients suffering from hypertension needs to be on treatment by these drugs for the whole lifetime. This kind of therapy necessitates that; the drugs are of high purity with very less impurity levels, so that the side effects are minimum. It also demands to produce these drugs at cheaper prices.

Objectives:

The objective of the present invention is to develop a process for manufacture of Metoprolol base and salts thereof, in high yields with higher purity and better operator friendly operations at cheaper prices.

Summary of the Invention:

This invention relates to an improved industrial process for manufacture of β-blocker, antihypertensive compounds more particularly Metoprolol base and salts thereof.

Detailed Description:

The present invention has made possible to produce metoprolol base and its salts in higher yields with high purity and avoiding processes like high vacuum distillation, at cheaper costs.

The present invention involves optimization of reaction temperatures, molar ratio of reactants in order to achieve higher purity and yields by avoiding purification of epoxide intermediates.

The present invention process involves three steps. In the first step is for preparation of epoxide by reacting 4-(2-methoxyethyl) phenol with epichlorohydrin in an aqueous media containing inorganic base such as sodium hydroxide at 40-45°C temperature.

The resultant epoxide is used in the second step for preparation of metoprolol base. The epoxide is treated with isoproplyamine in aqueous media to obtain Metoprolol base of high purity in high yields. The last step is converting metoprolol base into the succinate and tartrate salts by reacting with acids like succinic acid or tartaric acid in solvent media such as acetone.

By following the present invention as described below, it has been made possible to produce metoprolol base and its salts in higher yields with high purity and avoiding processes like high vacuum distillation, at cheaper costs.

The present invention involves optimization of reaction temperatures, molar ratio of reactants in order to achieve higher purity and yields by avoiding purification of epoxide intermediates.

It involves three steps :

Step- I : Epoxide formation by reacting 2-(methoxyethyl) phenol with epichlorohydrin.
Step-2 : Metoprolol base from reaction of epoxide with isopropyl amine.
Step- 3 : Metoprolol salts from metoprolol base

The process of the present invention is illustrated by the following example.

Step- I : Epoxide formation :

4-(2-methoxyethyl) phenol and epichlorohydrin are reacted in aqueous media like water, in presence of inorganic base such as sodium hydroxide, at temperature range of 40° - 45°C in 3 to 5 hours time.
The molar ratio of 4-(2-methoxyethyl) phenol to epichlorohydrin used in the range of 1 : 0.92 to 1 : 2.0, wherein the more preferred ratio is 1 : 1.1 to 1 : 1.4 and the most preferred ratio is 1 : 1.31.

Most preferred concentration of sodium hydroxide in water is 25% w/v

Preferred molar ratio of sodium hydroxide to 4-(2-methoxyethyl) phenol used is 1.14 : 0.95, more preferred is 1.024 : 1 and the most preferred ratio is 1.136 : 1

Reaction is carried out in the temperature range of 10° to 45°C, where in most preferred is 40° to 45°C.

Most preferred ratio of 4-(2-methoxyethyl) phenol : water is 1 : 1.6 volumes.

At the end of reaction, aqueous and organic phases are separated out.

The organic phase is washed thrice by water. The pH of washing must be in the range of 7 to 8. This pH range is necessary to achieve high purity of the epoxide.

Traces of water are removed from organic phase by distillation under vacuum below 55°C temperature. Keep the residue at 55°C, under vacuum for 3 to 5 hours, till the purity of sample is achieved in the range of 96-98%

The yield of the epoxide, so obtained is in the range of 93-95% of stoicheometric and purity 97-99%.

The epoxide with above purity is used for making metoprolol base.

Step-2 : Metoprolol base

The epoxide and isopropyl amine are reacted in aqueous media like water at temperature 0° - 30°C.

Preferred temperature during addition of epoxide is 10° to 25°C, while the most preferred temperature for completion of reaction is 30°C

Reaction completes in 3 hours time at 30°C.

Preferred molar ratio of epoxide : isopropyl amine is 1 : 5.0 – 5.5 where in the most preferred ratio is 1 : 5.2 - 5.3

Ratio of water to epoxide is 2 : 1 vol. : wt.

On completion of reaction, the reaction mixture is cooled to 0° – 5°C.

In order to achieve high purity it is necessary to maintain above temperature range. Formation of impurity at RRT 0.35 (By GC) is minimized by operating at 0° - 5°C. It is observed that in cases temperature rises above the range, this impurity increases.

The reaction mass is quenched by 2.25 volume of water. The product is extracted by 3 volumes of toluene. The toluene layer is washed three times by water for removal of isopropyl amine content is less than 0.5%.

Traces of isopropyl amine are removed by maintaining under vacuum below temperatures 25°C. It is necessary to eliminate traces of isopropyl amine at low temperature below 25°C, as the presence of isopropyl amine during distillation of toluene above 25°C leads to the formation of an impurity at RRT 1.54 by (GC). Following the present invention process this impurity formation is avoided.

In case when isopropyl amine remained in the traces, the impurity at RRT 1.54 (by GC) is detected.

Thus, following process as per present invention, formation of the impurities at RRT 0.35 & RRT 1.54 are under control, which leads to yield highly pure Metoprolol base in higher yields.

The analysis of sample of toluene layer shows absence of isopropyl amine. Toluene is distilled out at temperature 30° - 40°C under vacuum.

The residue of metoprolol base so obtained shows purity more than 99% and the yield of which is in range of 88 to 89%. (Stoicheometric)

Step- 3 : Metoprolol salts from metoprolol base

Metoprolol succinate :

Metoprolol base was converted to Metoprolol succinate, by reacting with succinic acid. The metoprolol base was dissolved in solvent such as acetone, at the temperature of 45±2°C. The succinic acid used in solution form the solution of succinic acid was prepared by refluxing in acetone. The succinic acid was used in stoichiometric proportion of 2 moles : 1 mole of metoprolol base.

The solution of succinic acid was added to the solution of metoprolol base. After mixing of the solution, pH of the reaction mass was adjusted 7.1 to 7.3. The reaction was carried out by refluxing for 4-5 hours. Then reaction mass was cooled to the temperature of 25±2°C and stirred at the temperature, followed by filtration. The metoprolol succinate so obtained was purified by crystallization from methanol.

Metoprolol succinate obtained with the yield of 72-75% (stoichiometric) having purity of more than 99.8% by HPLC and any other impurity less then 0.1%.

Metoprolol tartrate :

The metoprolol base was reacted with tartaric acid to obtain metoprolol tartrate salt. Metoprolol base was dissolved in suitable solvent such as acetone, at the temperature of 45±2°C. Tartaric acid was dissolved in solvent like acetone under refluxing conditions. The tartaric acid used in the molar ratio of 1 : 2 moles of metoprolol base. The solution of tartaric acid was added to the solution of metoprolol base and the pH was adjusted between 6.1 to 6.3

Reaction was refluxed for 4 hours for completion of salt formation, then cooled and stirred at 25±2°C for 2 hours. Metoprolol tartrate was obtained by filtration, which was then purified by crystallization from solvent like isopropanol. The metorprolol tartrate

obtained in the yield of 72-73% (stoichiometric) with purity of more than 99.8% and any other single impurity NMT 0.1%

EXAMPLES: METOPROLOL BASE FORMATION:

STEP – I: Epoxide preparation:

Example – 1:

200 gm (1.31 mole) 4 -(2 – methoxy ethyl) phenol was reacted with 159.45 gm (1.72 mole) epichlorohydrin, in presence of sodium hydroxide 59.80 gm (1.49 mole) in 320 ml water. The reaction mass was heated to 40 – 45°c for 5 – 6 hours. At the end of reaction, the aqueous phase was separated and the organic phase was washed with water to bring pH in the range of 7 – 8. The traces of water were removed by distillation under vacuum below 55°c. The epoxide was maintained under vacuum below 55°c temperature for 3 – 5 hours to get the purity in the range of 96 – 98%. The yield of Epoxide obtained is 254 – 260 gm (93 - 95%) with purity of 97 – 99% by HPLC.

Example – 2:

200 gm (1.31 mole) 4 -(2 – methoxy ethyl) phenol was reacted with 170.40 gm (1.84 mole) epichlorohydrin, in presence of sodium hydroxide 59.80 gm (1.49 mole) in 320 ml water. The reaction mass was heated to 40 – 45°c for 5 – 6 hours. At the end of reaction, the aqueous phase was separated and the organic phase was washed with water to bring pH in the range of 7 – 8. The traces of water were removed by distillation under vacuum below 55°c. The epoxide was maintained under vacuum below 55°c temperature for 3 – 5 hours to get the purity in the range of 96 – 98%. The yield of Epoxide obtained is 240 – 246 kg (88 - 90%) with purity of 97 – 99% by HPLC.

Example – 3:

200 gm (1.31 mole) 4 -(2 – methoxy ethyl) phenol was reacted with 121.71 gm (1.31 mole) epichlorohydrin, in presence of sodium hydroxide 53.89 gm (1.34 mole) in 320 ml water. The reaction mass was heated to 40 – 45°c for 5 – 6 hours. At the end of reaction, the aqueous phase was separated and the organic phase was washed with water to bring

pH in the range of 7 – 8. The traces of water were removed by distillation under vacuum below 55°c temperature. The epoxide was maintained under vacuum below 55°c temperature for 3 – 5 hours to get the purity in the range of 96 – 98%. The yield of Epoxide obtained is 218 – 232 kg (80 - 85%) with purity of 97 – 99% by HPLC.

Example – 4:

200 gm (1.31 mole) 4 -(2 – methoxy ethyl) phenol was reacted with 159.45 gm (1.72 mole) epichlorohydrin, in presence of sodium hydroxide 59.80 gm (1.49 mole) in 320 ml water. The reaction mass was heated to 30 – 35°c and maintained for 17 hours. At the end of reaction, the aqueous phase was separated and the organic phase was washed with water to bring pH in the range of 7 – 8. The traces of water were removed by distillation under vacuum below 55°c. The epoxide was maintained under vacuum below 55°c temperature for 3 – 5 hours to get the pure epoxide. The yield of Epoxide obtained is 213 gm (78 %) with purity of 82.57% by HPLC.

STEP – II: Metoprolol Base Preparation

Example – 1:

250 gm (1.20mole) Epoxide (from example-1 step – I) was added in the solution of 355 gm (6.01 mole) iso propyl amine in 500 ml water at 10°c temperature. The reaction was maintained further at 30°c for three hours. After cooling the reaction mass to 10 – 15°c, was quenched in 565 ml of water. The product was extracted in toluene (750 ml). The toluene layer was washed with water to remove excess of iso propyl amine and bring the limit of iso propyl amine below 0.5%. Traces of iso propyl amine were removed under vacuum below 25°c. The toluene layer was concentrated under vacuum at 30 – 40°c. The yield of metoprolol base was 282 – 285 gm (88 – 89%) with purity of 99% by HPLC.

Example – 2:

225 gm (1.08 mole) Epoxide (from example-2 step – I) was added in the solution of 351 gm (5.95 mole) iso propyl amine in 450 ml water at temperature of 10°c. The reaction was maintained further at 30°c for three hours. After cooling the reaction mass to 10 – 15°c, was quenched in 506 ml of water. The product was extracted in toluene (675 ml).

The toluene layer was washed with water to remove excess of iso propyl amine and bring the limit below 0.5%. Traces of iso propyl amine were removed under vacuum below 25°c. The toluene layer was concentrated under vacuum at 30 – 40°c. The yield of metoprolol base was 254 – 257 kg (88 – 89%) with purity of 97 – 99% by HPLC.

Example – 3:

225 gm (1.08 mole) Epoxide (from example-3 step – I) was added in the solution of 319.10 gm (5.00 mole) iso propyl amine in 450 ml water at temperature of 10°c. The reaction was maintained further at 30°c for three hours. After cooling the reaction mass to 10 – 15°c, was quenched in 506 ml of water. The product was extracted in toluene (675 ml). The toluene layer was washed with water to remove excess of iso propyl amine and bring the limit below 0.5%. Traces of iso propyl amine were removed under vacuum below 25°c. The toluene layer was concentrated under vacuum at 30 – 40°c. The yield of metoprolol base was 245 – 251 kg (85 – 87%) with purity of 97 – 99% by HPLC.

STEP - III: SALT FORMATION:

Example – 1:

267 gm metoprolol base (from example-1 step – II) was dissolved in 1870 ml of acetone and heated to 45°c. After charcoalisation and filtration at 45°c, the reaction mass was heated to reflux. Adjust the pH of the reaction to 7.1 – 7.3 using succinic acid solution prepared by dissolving 59.045 gm succinic acid in 1140 ml acetone at reflux. Maintain the reaction at reflux for 4 hours. Cool the reaction to 26°c and maintain 2 hours. The precipitated salt was filtered to get crude metoprolol succinate. The crude product was purified by crystallization in 800 ml methanol. The filtered product was dried to yield 277 – 288 gm (72 – 75 %) with purity of more than 99.8% by HPLC and any other impurity less than 0.1%.

Example – 2:

267 gm metoprolol base (from example-1 step – II) was dissolved in 1870 ml of acetone and heated to 45°c. After charcoalisation at 45°c for 30 minutes and filtration, the

reaction mass was heated to reflux. Adjust the pH of the reaction to 6.1 – 6.3 using tartaric acid solution prepared by dissolving 75.045 gm tartaric acid in 1350 ml acetone at reflux. Maintain the reaction at reflux for 4 hours. Cool the reaction to 26°c and maintain 2 hours. The precipitated salt was filtered to get crude metoprolol tartrate. The crude product was purified by crystallization in 2400 ml iso propyl alcohol. The filtered product was dried to yield 300 – 305 gm (72 – 73 %) with purity of more than 99.8% by HPLC and any other impurity less than 0.1%.

We claim

1. An improved industrial process for manufacture of metoprolol base and salts thereof, wherein, the said process comprises of

    a) preparation of metoprolol base and

    b) preparation of metoprolol salts

wherein, the said process for the preparation metorpolol base comprises,

i) preparation of epoxide by reacting 4-(2-methoxy ethyl) phenol and epichlorohydrin in aqueous media like water, in presence of inorganic base such as sodium hydroxide at a temperature range of 10 - 45°C upto more than 3 hours,

separating the aqueous phases and organic phases at the end of the reaction,

washing the organic phase repeatedly with water, maintaining the pH between 7-8,

removing the traces of water from organic phase by azeotropic distillation under vacuum below 55° C for 3-5 hours and

drying the residue at 55° C under vacuum for 3 to 5 hours, to achieve the high purity and further

ii) conversion of the epoxide into metoprolol base by treating with isopropyl amine in aqueous media like water at temperature 0-30° C upto 3 hours,

cooling the reaction mass to 0-5° C to achieve the high purity,

quenching the reaction mass with water,

extracting the product with toluene,

washing the toluene layer with water,

removing the traces of isopropyl amine under vacuum below 25°C to avoid the formation of impurity in the product and

toluene is distilled out under vacuum at temperature 30 – 40°C to obtain metoprolol base in high yield and purity.

2. An improved industrial process for manufacture of metoprolol base as claimed in claim 1 wherein the molar ratio of 4-(2-methoxyethyl) phenol to epichlorohydrin is in the range of 1:0.92 to 1:2.0.

3. An improved industrial process for manufacture of metoprolol base as claimed in claim 1 wherein the molar ratio of 4 (2-methoxyethyl) phenols to epichlorohydrin is in the range of 1:1.1 to 1:1.4.

4. An improved industrial process for manufacture of metoprolol base as claimed in claim 1 wherein the molar ratio of 4(2-methoxyethyl)phenol to epichlorohydrin is in the ratio of 1:1.31

5. An improved industrial process for manufacture of metoprolol base as claimed in claim 1 wherein the molar ratio of sodium hydroxide to 4-(2-methoxyethyl) phenol is used in the range of 1.14:0.95 to 1.024:1.0.

6. An improved industrial process for manufacture of metoprolol base as claimed in claim 1 wherein the molar ratio of sodium hydroxide to 4-(2-methoxyethyl) phenol is used in the ratio of 1.136:1.

7. An improved industrial process for manufacture of metoprolol base as claimed in claim 1 wherein concentration of sodium hydroxide in water is 25% w/v.

8. An improved industrial process for manufacture of metoprolol base as claimed in claim 1 wherein the molar ratio of 4-(2-methoxyethyl) phenol : water is 1:6 volumes.

9. An improved industrial process for manufacture of metoprolol base as claimed in claim 1 wherein the said reaction is carried out in the temperature range of 40 to 45° C.

10. An improved industrial process for manufacture of metoprolol base as claimed in claim 1 wherein temperature during the addition of epoxide to isopropyl amine is 10° to 25°C.

11. An improved industrial process for manufacture of metoprolol base as claimed in claim 1 wherein the temperature for completion of reaction is 30° C in 3 hours.

12. An improved industrial process for manufacture of metoprolol base as claimed in claim 1 wherein molar ratio of epoxide : isopropyl amine is 1 : 5.0 – 5.5.

13. An improved industrial process for manufacture of metoprolol base as claimed in claim 1 wherein molar ratio of epoixde: isopropyl amine is 1: 5.2 - 5.3.

14. An improved industrial process for manufacture of metoprolol base as claimed in claim 1 wherein ratio of water to epoxide is 2: 1 vol : wt.

15. An improved industrial process for manufacture of metoprolol base as claimed in claim 1 wherein the reaction mass is quenched with 2.25 volume of water and the product is extracted by 3 volumes of toluene.

17. An improved industrial process for manufacture of metoprolol base as claimed in claim1 wherein the toluene layer is washed 1 to 5 times with water to remove isopropylamine content to less than 0.5%.

18. An improved industrial process for manufacture of metoprolol base as claimed in claim 1 wherein toluene is distilled out under vacuum at temperature 30– 40°C to obtain metoprolol base.

19. An improved industrial process for manufacture of metoprolol base and salts thereof as claimed in claim 1(b) wherein, the said process for preparation of metoprolol succinate salt comprises

i) dissolving the metoprolol base in seven volumes of acetone and heated at 45°C,

ii) after charcoalization filter the said reaction mixture at 45°C,

iii) the said reaction mass is heated to reflux,

iv) preparing the solution of succinic acid in stoicheometric proportion to metoprolol in 1:2 ratio in twenty volumes of acetone by refluxing,

v) adding the succinic acid solution to metoprolol base solution by adjusting the pH of the said reaction mixture at 7.1-7.3,

vi) refluxing the reaction mixture for 4-5 hours,

vii) cooling the reaction mixture to 26° C,

viii) maintaining the same temperature of the reaction mixture with stirring for two hours,

ix) filtering the metoprolol succinate salt,

x) crystallizing the metoprolol succinate salt and

xi) metoprolol succinate salt is purified with three volume of methanol to obtain the (Stoicheometric)yield 72-75% with a purity of 99.8%.

20. An improved industrial process for manufacture of metoprolol base and salts thereof as claimed in claim 1 (b) wherein, the said process for preparation of metoprolol tartrate salt comprises

i) dissolving the metoprolol base in seven volumes of acetone,

ii) adding the activated charcoal,

iii) heating to 45°C,

iv) stirring for 30 minutes,

v) filtering the charcoal,

vi) preparing the solution of tartaric acid in acetone by dissolving tartaric acid in stoicheometric proportion of 1:2 (metoprolol base) in 18 volumes of acetone by refluxing,

vii) adding the tartaric acid solution to metoprolol base solution under refluxing condition by adjusting the pH between 6.1-6.3,

viii) refluxing the reaction mixture for 4 hours,

ix) cooling to 26°C,

x) stirring the reaction mixture at 26°C for 2 hours,

xi) filtering the metoprolol tartrate and

xii) the metoprolol tartrate is crystallized from nine volumes of isopropyl alcohol to obtain (Stoicheometric) yield 72-73% with purity 99.8% by HPLC.

20. An improved industrial process for manufacture of metoprolol base and salts thereof claimed in claim 1 (b), 19 and 20 wherein metoprolol salts obtained by the claimed process have no impurity more than 0.1 %.

21. An improved industrial process for manufacture of metoprolol base and salts thereof substantially described herein with reference to the foregoing examples.

Dated this 7th Day of Jan 2004

Dr. GOPAKUMAR G. NAIR
Agent for the Applicant

HAL